

### **REMARKS**

Claims 1-3, 7-12, and 20-23 are pending in the application. It is noted that the Office Action Summary erroneously states that claims 11-12 are not pending in the application, although these claims have been indicated to be free of the prior art. The Office Action Summary also erroneously states that claim 14 is rejected. Claim 14 was previously cancelled. Reconsideration of the claims in view of the following Remarks is requested.

### **Withdrawn Rejections/Objections**

Applicants acknowledge the withdrawal of the objections to the specification. Applicants acknowledge the withdrawal of the rejection of claims 1-3 and 5-14 under 35 U.S.C. 112, second paragraph. Applicants acknowledge the withdrawal of the rejection of claims 1-2, 4-5, and 8-9 under 35 U.S.C. 102(e) over Wrighton et al.

### **35 USC § 103**

Claims 1-3, 7-10, and 20-23 were rejected under 35 U.S.C. 103(a) as unpatentable over Wrighton et al. for reasons advanced in the last Office Action. Applicants traverse this rejection.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: (1) the reference must teach or suggest all of the claim limitations; (2) there must be a suggestion or motivation, either in the reference itself or in the knowledge generally available to one of skill in the art to modify the reference; and (3) there must be a reasonable expectation of success. Applicants submit that not all of these requirements have been met because in the least the reference does not disclose all of the claim limitations, and there is no suggestion or motivation to modify the reference to disclose all of the claim limitations.

Independent claim 1 is directed to an isolated library of structurally constrained cyclic peptides, wherein A2 is amino acid W and A4 is W or L. Applicants submit that Wrighton et al. nowhere discloses an isolated library as claimed comprising W at the position corresponding to A2 and W or L at position A4 of the present claims. Rather, in the preferred embodiments disclosed in Wrighton et al., X5 of Wrighton et al., which corresponds to A2 of Applicants' claims, is limited to M, F, or I.

In response, the Examiner contends that Figure of Wrighton et al. teaches a phagemid mutagenesis library, wherein the positions within the cysteine residues were mutated to any other amino acid at a frequency of 50%. The Examiner asserts, therefore, that position 2 would be Trp in some embodiments, since it is expected that the residues between the cysteine residues would be any of the 20 naturally occurring amino acids including Trp. The Examiner also asserts that the disclosure of Wrighton of replacing the amino acid at that position would provide motivation to make the modification. Applicants respectfully disagree.

"The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that claim obvious." (*In re Baird*, 29 USPQ2d (Fed. Cir. 1994). A *prima facie* case of obviousness requires that "one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus." MPEP 2144.08(II)(A)(4).

Applicants submit that one of skill in the art would not have been motivated to select the presently claimed subgenus, wherein A2 is W and A4 is W or L, in light of the teachings of Wrighton et al. The present invention is directed to an isolated library of structurally constrained peptides. Wrighton et al., however, is directed to identifying agonists of EPO. Applicants have discovered that an isolated library as claimed, wherein A2 is W and A4 is W or L, is useful in stabilizing  $\beta$ -turn hairpin structures. Wrighton et al. nowhere teaches or suggests that a peptide having W at the position corresponding to A2 in Applicants' claims would be advantageous in generating an EPO agonist, or an isolated library for presenting a  $\beta$ -turn hairpin structure, or for any other reason. There is no discussion in Wrighton et al. of the desirability of forming a trp-trp or trp-leu cross-strand pair between A2 and A4 in order to enhance hairpin stability. The Wrighton et al. reference does not teach or suggest the ability of the isolate library of structurally constrained cyclic peptides as claimed by Applicants to accommodate a number of different types of turn structures or that the stability of the turn sequences would be enhanced.

The Examiner asserts, however, that it would be within the ordinary skill in the art to use a Trp at position 2 as recited in the present claims, because Wrighton et al. discloses a Trp at position 2 in Table 8 (SEQ ID 89). Applicants respectfully disagree. The question under 35 U.S.C. § 103 is not whether the differences between the claimed invention and the prior art would have been obvious, but whether the claimed invention *as a whole* would have been obvious. MPEP 2144.08(I)(A)(2.) The present claims are not limited merely by the amino

acids at position A2 and A4, but also recite that the amino acids at positions A1 and A5 are W, Y, F, H, I, V, or T. SEQ ID 89, however, has the amino acid E at the position corresponding to A1 of the present claims. Applicants submit, therefore, that SEQ ID 89 is not a species falling within the presently claimed genus.

Indeed, the sequences of Table 8 are derived not from the mutagenesis library of Figure 3, but rather from the library of Figure 4B. The mutagenesis fusion proteins resulting from this library were also panned on immobilized EPO-R (column 13, lines 29-31). Table 8 of Wrighton et al. lists the preferred peptides resulting from this panning process. Applicants submit that none of the peptides in Table 8 fall within the presently claimed subgenus.

Moreover, Applicants submit that one of skill in the art would not be motivated to select W at position A2 over any of the other amino acids. Applicants submit that of the peptides identified in libraries where tyrosine, glycine-proline and threonine-tryptophan were fixed including those exemplified in Table 6 (library of Fig. 3), Table 7 (library of Fig. 4A), Table 8 (library of Fig. 4B), Table 9 (library of Fig. 4C), Table 10 (library of Fig. 5) and Table 11 (library of Fig. 6), at least 16 other amino acids could be found at the position corresponding to A2. Thus, one of skill in the art would not be motivated to select tryptophan at that position from any other amino acid, which can occur at that position.

Furthermore, as discussed previously, the Wrighton et al. reference specifies that the preferred embodiments have a M, I or F at the position corresponding to A2. Thus, the disclosure of Wrighton et al of these preferred embodiments would lead one of skill in the art to make different substitutions at this position than those claimed by Applicants and provides evidence of the nonobviousness of Applicants' claims. In re Baird at 1552.

The Examiner contends, however, that one of skill would be motivated to substitute the A2 position of Wrighton et al. with all natural amino acids, including trp, because doing so would facilitate identification of lead compounds from the library. Applicants respectfully submit that the Examiner's reasoning represents an improper "obvious to try" rationale for modifying the prior art reference. As discussed above, some motivation to select the claimed subgenus over other members of the prior art genus must be found to support a *prima facie* case of obviousness. A mere assertion that it would be beneficial to vary all parameters within a genus until a successful result is achieved represents an improper "obvious to try" rationale, and does not supply the necessary motivation to modify the prior art. *MPEP 2145(X)(B)* (citing *In re*

*O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)). In the context of a genus-subgenus relationship, "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success." *MPEP 2144.08(II)(A)* (quoting *Hodosh v. Block Drug Co.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)). Applicants submit that the Examiner has not articulated any reason why Applicants' claimed subgenus should be selected from the prior art genus over any other subgenus, or that there would be a reasonable expectation of success in doing so.

Applicants submit, therefore, that claims 1-3, 7-10, and 20-23 are patentable over *Wrighton et al.* under 35 U.S.C. 103, at least for the foregoing reasons. Withdrawal of the rejection is therefore requested.

#### Request for an Interview

Applicants request an interview with the Examiner and her supervisor. Applicants request that the Examiner contact Applicants' representative to schedule an interview.

#### SUMMARY

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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